PERNICIOUS ANEMIA: ADEQUATE versus OPTIMUM TREATMENT

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ADDISONIAN pernicious anemia is essentially a complex deficiency disease. Meulengracht says that the veil of mystery surrounding the disease has been torn down, but many features still remain unexplained.

We know that it is a disorder characterized by changes in the hematopoietic, nervous and gastrointestinal systems, brought about by a defective physiology which leads to the loss of an essential ultimate liver principle. We say ultimate, because it is dependent upon an interaction between a food and stomach factor. The substance resulting from this interaction is converted somewhere between the stomach and the liver into the ultimate liver principle.

PATHOLOGY

The failure of formation of this liver principle is due to a primary functional secretory failure of the gastric and duodenal glands which secrete Castles intrinsic factor. This secretion failure is probably due to a genetic or hereditary fault and cannot be corrected.

This leads to the secondary liver deficiency, which is merely one of storage, and can be corrected.

Although other organs, as kidneys and brain, store antianemic material, this material is not identical with the liver principle. Whether or not these other organs are depleted in relapse as is the liver, is not known. The lesions that occur in pernicious anemia may be regarded as those that arise from a shortage of the liver principle itself, and those that arise from other shortages usually in vitamins.

We may visualize Addisonian pernicious anemia as developing after years of anacidity with a gradual loss of the stomach intrinsic factor, then a gradual reduction of the specific liver principle. The reduction of the liver principle then leads to the characteristic blood and nerve changes, but often in totally unparallel degrees. There may be grave anemia in one individual with little or no nerve lesions; there may be crippling neural degeneration in another with no reduction in the normal blood level. The blood changes, regardless of the degree of anemia, practically always respond to administration of enough liver extract. The nervous system lesions, however, may be irreparable. Treatment will improve the majority, but in certain cases there will occur merely arrest of the damage. In the long period before signs and symptoms become manifest, it is, perhaps, unavoidable that complicating vitamin deficiencies should develop. Anorexia, one of the first symptoms of pernicious anemia, often leads to under nutrition and, in Southern California at least, to bizarre diets. The long standing anacidity, and the impaired intestinal absorption, complete the perfect combination for the development of avitaminosis. In the patients in acute relapse it is not uncommon not to see the smooth, pale atrophic tongue due to liver deficiency alone, but to see the red tongue due to B avitaminosis.

We have recently seen a patient, with known pernicious anemia for eight years, develop synchronously with an acute relapse a full-blown picture of pellagra. It is probable that, in relapse, in addition to the changes ascribable to the dearth of the specific liver principle, there are varying degrees of thiamin, riboflavin, nicotinic acid and other B complex deficiencies.

In such a disease arising from the gradual depletion of the body of essential materials, the indications for treatment are obvious. First, preventive treatment should entail the recognition of the disease early before the depletion is marked, and before grave nerve tissue damage has occurred. This will allow early correction of the deficiency.

DIAGNOSIS

How can we recognize cases early? We may either seek them out among the relatives of the patients, or we may suspect them as they are seen early masquerading as other conditions. The increasing evidence which is accumulating, to prove that Addisonian pernicious anemia is due to an hereditary fault, can help us to recognize potential cases. We may look for such cases especially among near relatives. Anacidity here may be an ordinary achlorhydria without hazard, but it also may be a precursor of later developing pernicious anemia. The risk of such a relative with anacidity getting pernicious anemia is much higher than the risk in an ordinary person.

We have found ten of sixty-one near relatives with histamine anacidity. Of the ten, four have developed incipient pernicious anemia, and we are suspicious of two more. None of the fifty-one with acid has developed any anemia. The risk of an ordinary person with achlorhydria developing pernicious anemia has been shown by Bloomfield to be only about one in three or four hundred.

The usual problem is that of early recognition in a person with no family history of the disease. The early symptoms may suggest avitaminosis; such as easy fatigue, anorexia, soreness of the tongue, some pain and tingling in the hands and feet; these symptoms, plus a mild anemia, may lead to the administration of a mixture of vitamins, iron and liver, which serves to keep the patient in fair health, but to prevent the true recognition and early adequate treatment of the disease. It is much preferable to withhold liver until the true type of anemia has been manifested, than to obtain temporary improvement and obscure the diagnosis. The therapeutic test with liver is justifiable in certain severe anemias; but liver should not be used in mild anemia until the

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diagnosis of pernicious anemia is made. Once the condition is recognized, how should it be treated? It should be by the complete, continuous correction of the specific liver deficiency and any ancillary vitamin deficiencies.

TREATMENT

In acute relapse where the liver depletion is complete, the correction should be quick. Once enough liver has been given, the immediate specific requirement has been satisfied, but often supportive treatment may be needed until the liver can be effective. The vomiting, dehydrated patient may need salt and water intravenously, while those with gravely low blood volume may need blood transfusion. This is rarely necessary and usually only in those with erythrocyte counts of below one million. Despite the probable invariable tendency to shortages of the B complex vitamins, as a rule it is not necessary to administer vitamins. Usually, the administration of liver alone leads to such an immediate increase in appetite and general food intake that any avitaminotic complications improve synchronously with the improvement of the anemia. It must be remembered that liver was the original source for most of the B vitamins.

It is now believed that the surest most economical way to correct the liver shortage is by injection of the ultimate substance itself, liver extract. Liver by mouth, or desiccated hog stomach by mouth, must undergo loss incident to absorption. How can we be sure we have corrected and are maintaining correction of liver deficiency? What amount of liver is needed and how often should it be given?

We have no precise objective data to tell us whether we are giving enough to return the liver storage to normal. Our present criteria for adequate treatment are not standards for producing a completely-stocked liver. This is understandable because, surprisingly enough, we do not know accurately how much the normal human liver stores, which would represent the amount the patient in relapse needs. Qualitative tests of human livers of patients in relapse before treatment, and of human livers after treatment, have shown that it is stored by such treatment; but no quantitative tests of normal human livers have been made.

By inference, if the human liver stores a similar amount to the beef liver we can postulate a primary deficiency of the principle of several hundred U.S.P. hematopoietic units. Beef liver contains 10-15 U.S.P. hematopoietic units per 100 gms. or 150-225 U.S.P. units per 1500 gms. of liver tissue. A normal human liver then, weighing 1500 gms., should store approximately 150-225 U.S.P. units. This, plus the amount needed by other body tissues in relapse, should represent an initial lack of several hundred units. The quick, complete, quantitative correction of this deficiency in relapse should elicit optimum results and its continuous correction should maintain optimum results.

In relapse, where irreparable nerve damage may occur rapidly, such a rapid, complete correction of the deficiency would seem essential.

To repeat and emphasize a thought, irreparable blood changes are quite rare, but irreparable nerve tissue damage is so common that prevention becomes of prime importance. Treatment which produces merely a satisfactory elevation in the erythrocyte count does not suffice. This can be achieved by a relatively small fraction of the amount representing the apparent real deficiency.

One U.S.P. hematopoietic unit a day for 60 days, in the average patient, will effect a satisfactory erythrocyte rise, but only 60 units shall have been supplied to a body apparently needing several hundred units.

This method of treatment has been considered adequate in the past. Recent authors, as Haden and West, have advocated giving 15 units daily for 1-2 weeks, then several times a week; the total amounting to approximately 300 U.S.P. units in 2 months, and entailing twenty or more injections. This is preferable to the former method; but again we may ask, Why give small repeated doses of 15 units to the body when it probably needs several hundred units? Why not attempt to correct it immediately? It has been argued that a large single dose is unphysiological, citing as an analogy thiamin deficiency, where large amounts cannot be stored. This, we believe, is a faulty analogy, as thiamin has no large storage organ for the deficient substance, and in pernicious anemia there is such a storage depot.

Can a large single dose be absorbed and not excreted? In another paper we have reported the details of 19 severe cases in relapse when patients were given large single doses of concentrated parenteral liver extract, varying from 150 to 400 U.S.P. units.† No oral or parenteral liver was given thereafter. The average red-cell count at the end of three months in these 19 patients was 4.7 million. The response in 16 of the 19 was in every way adequate. In 3, the improvement was marked, but not satisfactory. One was 86, the other two had symptoms and signs suggestive of bleeding gastro-intestinal lesions. The response of neurologic signs and symptoms was excellent. Incapacitation due to ataxia was relieved, paresthesias were improved and the response was in every way adequate. There was no evidence that the concentrated liver extract failed in anything that crude liver extract would have done. Whether a patient in relapse needs 150 or 400 U.S.P. units, we do not know. Until we have precise data, the amount used in the initial dose must be experimental. We are justified in assuming that a massive initial dose is as satisfactory in the majority of cases in relapse as are small repeated doses.

PROCEDURE AT LOS ANGELES COUNTY GENERAL HOSPITAL

The tentative treatment of patients in the Outside Medical Relief Service of the Department of

Charities of Los Angeles County, has been as follows: 1 cc. of a concentrated liver extract. containing 15 U.S.P. hematopoietic units, is injected in the muscle of the buttock. In the absence of any reaction, the next day 9 cc. are injected. This furnishes liver containing 150 U.S.P. units. One month later, and at monthly intervals, liver extract containing 30 U.S.P. units is given. The patient is given a general diet. Any vitamin needs are usually supplied both by the liver and by the diet itself. If gastro-intestinal symptoms persist after the blood count is normal, we give diluted hydrochloric acid. We rarely find this necessary. Practically all our patients have done well without medicinal iron. Occasionally it is necessary.

Further work upon the quantitative storage of the antipernicious anemia substance in the liver is being done. We wish here merely to submit the thought that the treatment of a deficiency disease, such as pernicious anemia, should be directed at correction of the fundamental deficiency, rather than at correction of the resulting signs and symptoms.†

SUMMARY AND CONCLUSIONS

1. Addisonian pernicious anemia is a complex deficiency disease, the ultimate deficiency of which is in the antianemic liver principle.

2. The quantitative correction of the liver deficiency must be the aim of treatment.

3. We feel that an initial massive dose to replenish this initial deficiency, followed by monthly doses to replenish the utilized material, is a rational procedure.

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COUNTY MEDICAL SOCIETY MEMBERSHIP: LEGAL SIGNIFICANCE

RECENT DECISION OF THE CALIFORNIA SUPREME COURT: IN KERN COUNTY MEDICAL SOCIETY CASE

FOREWORD.—In the year 1935, a member of the Kern County Medical Society was cited to appear before that component unit of the California Medical Association, and after trial, was expelled from membership. The member so expelled presented an appeal to the California Medical Association and the Council of that body, after due consideration, upheld the action of the Kern County Medical Society. Appeal to the Judicial Council of the American Medical Association was then submitted by the member. After hearing, the Judicial Council of the A. M. A. sustained the judgment of its constituent state association, and the latter's component county unit.

The member then filed an action in the Superior Court of Kern County, praying that the action of the Kern County Medical Society be set aside. However, the Superior Court upheld the Kern County Medical Society. Appeal was then taken by the member to the Fourth District Court of Appeal of the State of California, which reversed the judgment of the Superior Court.

A proceeding in mandamus was then filed by the member in the Supreme Court of the State of California to compel his reinstatement to membership in the Kern County Medical Society. The appeal was granted a hearing and on January 12, 1942, the Supreme Court handed down its decision, in which the judgment of the Superior Court was affirmed. Thus, the reversal judgment of the Fourth Appelate district was not sustained. The action of the Kern County Medical Society in expelling the member is upheld.

For editorial comment, see page 59.

Because it is desirable that the opinion of the Supreme Court be made a matter of record in a medical publication, the decision of the Supreme Court of the State of California appears below.

(COPY)

SMITH *v.* KERN COUNTY MEDICAL ASSOCIATION

[L. A. No. 17336. In Bank. Jan. 12, 1942.]

JOE K. SMITH, M.D., Appellant, v. KERN COUNTY MEDICAL ASSOCIATION (an Unincorporated Association) et al., Respondents.

[On hearing after decision by the District Court of Appeal, Fourth Appellate District. Civ. No. 2504. 44 A. C. A. 323, 112 P. (2d) 268, reversing judgment of the Superior Court. Judgment affirmed.]

[1] *Associations—Intervention of Court—Expulsion—Function Performed.*—In any proper case involving the expulsion of a member from a voluntary unincorporated association, the only function which the courts may perform is to determine whether the association has acted within its powers in good faith, in accordance with its laws, and the law of the land.

[2] *Id.—Intervention by Court—Expulsion—Sufficiency of Evidence.*—In a mandamus proceeding to compel the reinstatement of a member of a medical society, findings that the amendments to the Constitution and by-laws relative to expulsion of members were regularly adopted, that the charges against the petitioner constituted a violation of the principles of ethics and laws of the society, and that the expulsory proceedings were regularly taken in good faith, etc., were supported by the evidence.

[3] *Id.—Expulsion—Presence at Hearing—Waiver.*—A member of a society may not complain that the hearing on the question of his expulsion was conducted in his absence where he had due notice and an opportunity to attend, but voluntarily absented himself.

[4] *Id.—Expulsion—Vote.*—In a mandamus proceeding to compel the reinstatement of a member of a society, a contention that the required two-thirds majority of membership did not vote for expulsion is without merit where the minutes of the society declare that those voting for expulsion constituted a two-thirds majority of those attending, and the member has not shown either that a quorum was not present or that the members voting did not constitute a majority.

[5] *Id.—Expulsion—Res Judicata.*—The termination by a medical society, without disciplinary action, of proceedings against a member for failure to resign from a hospital staff while certain conditions persisted, does not preclude an accusation in a subsequent year predicated on nonresignation, since the basis of the charge is of a continuing nature.

† Much of this liver extract was supplied by the Eli Lilly and Company, Indianapolis, Indiana.